L1 ANSWER 1 OF 3 MEDLINE
AN 1998102968 MEDLINE
DN 98102968 PubMed ID: 9439794
TI Mechanism and prevention of neurotoxicity caused by **beta-amyloid** peptides: relation to Alzheimer's disease.
AU Blanchard B J; Konopka G; Russell M; Ingram V M
CS Department of Biology, Massachusetts Institute of Technology, Cambridge 02139, USA.
SO BRAIN RESEARCH, (1997 Nov 21) 776 (1-2) 40-50.
Journal code: 0045503. ISSN: 0006-8993.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199802
ED Entered STN: 19980306
Last Updated on STN: 19980306
Entered Medline: 19980224
AB In Alzheimer's disease, neurotoxic **beta-amyloid** peptides cause a deleterious influx of calcium ions into neurons. This increase in [Ca2+]int is expected to trigger intracellular events that eventually cause cell dysfunction and cell death. We find that the aggregated **beta-amyloid** peptide **beta** AP25-35 opens irreversibly a Ca(2+)-carrying channel, as does aggregated **beta** AP1-42. The opening of this channel is unaffected by DL-AP5, but it is blocked by Mg2+, CNQX and DNQX, suggesting a non-NMDA channel. External calcium enters and cytosolic calcium levels rise several-fold, as measured by fura-2 ratiometric analysis. Our findings illustrate a very early molecular event in the neurotoxicity of Alzheimer's disease. To combat the neurotoxic effect of aggregated **beta-amyloid** peptides, we have devised a series of very short antagonistic peptides. Using a combinatorial library of hexapeptides made from **D-amino acids**, we have selected peptides by their ability to complex with the tagged **beta-amyloid** peptide **beta** AP25-35. Certain of these so-called 'decoy peptides', as well as some modified decoy peptides, are able to abolish the calcium influx caused by aggregated, probably fibrillar, **beta-amyloid** peptides **beta** AP25-35 and **beta** AP1-42.

L1 ANSWER 2 OF 3 MEDLINE
AN 97284736 MEDLINE
DN 97284736 PubMed ID: 9139713
TI Controlling **amyloid beta**-peptide fibril formation with protease-stable ligands.
CM Erratum in: J Biol Chem 1997 Jul 11;272(28):17894
AU Tjernberg L O; Lilliehook C; Callaway D J; Naslund J; Hahne S; Thyberg J; Terenius L; Nordstedt C
CS Laboratory of Biochemistry and Molecular Pharmacology, Section of Drug Dependence Research, Department of Clinical Neuroscience, Karolinska Hospital, S-171 76 Stockholm, Sweden.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 May 9) 272 (19) 12601-5.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199706
ED Entered STN: 19970630
Last Updated on STN: 20000303
Entered Medline: 19970616
AB We have previously shown that short peptides incorporating the sequence KLVFF can bind to the approximately 40amino acid residue Alzheimer

amyloid beta-peptide (Abeta) and disrupt **amyloid** fibril formation (Tjernberg, L. O., Naslund, J., Lindqvist, F., Johansson, J., Karlstrom, A. R., Thyberg, J., Terenius, L., and Nordstedt, C. (1996) J. Biol. Chem. 271, 8545-8548). Here, it is shown that KLVFF binds stereospecifically to the homologous sequence in Abeta (i.e. Abeta16-20). Molecular modeling suggests that association of the two homologous sequences leads to the formation of an atypical anti-parallel **beta**-sheet structure stabilized primarily by interaction between the Lys, Leu, and COOH-terminal Phe. By screening combinatorial pentapeptide libraries exclusively composed of **D-amino acids**, several ligands with a general motif containing phenylalanine in the second position and leucine in the third position were identified. Ligands composed of **D-amino acids** were not only capable of binding Abeta but also prevented formation of **amyloid**-like fibrils. These ligands are protease-resistant and may thus be useful as experimental agents against **amyloid** fibril formation in vivo.

L1 ANSWER 3 OF 3 MEDLINE
AN 96428572 MEDLINE
DN 96428572 PubMed ID: 8831674
TI Inhibition of Alzheimer's amyloidosis by peptides that prevent **beta**-sheet conformation.
AU Soto C; Kindy M S; Baumann M; Frangione B
CS Department of Neurology, New York University Medical Center, New York 10016, USA.. Claudio.Soto@mcfpo.med.nyu.edu
NC AG05891 (NIA)
AG08721 (NIA)
AG10953 (NIA)
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1996 Sep 24) 226 (3) 672-80.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199611
ED Entered STN: 19961219
Last Updated on STN: 19980206
Entered Medline: 19961107
AB **Amyloid beta**-peptide (A **beta**) is a major fibrillar component of neuritic plaques in Alzheimer's disease (AD) brains and is related to the pathogenesis of the disease. We hypothesized that **amyloid** formation could be inhibited by peptides homologous to A **beta** (position 17-21) with a similar degree of hydrophobicity, but with a very low propensity to adopt a **beta**-sheet conformation by incorporating proline residues (anti-**beta**-sheet peptides or **beta**-sheet inhibitors). An 11-residue peptide with these characteristics binds to A **beta**, inhibits A **beta** fibril formation and partially disaggregates preformed fibrils in vitro. Shorter anti-**beta**-sheet peptides and analogs containing **D-amino acids** are also able to inhibit A **beta** fibrillogenesis. The latter are more resistant to proteolytic degradation and may serve as a starting point to design more efficient peptides derivatives to inhibit amyloidogenesis in vivo.

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L7 ANSWER 1 OF 7 MEDLINE
AN 2002366817 IN-PROCESS
DN 22106566 PubMed ID: 12111445
TI Potential neurotoxic inflammatory responses to Abeta vaccination in humans.
AU Munch G; Robinson S R
CS Neuroimmunological Cell Biology Unit, Interdisciplinary Centre for Clinical Research (IZKF), University of Leipzig, Federal Republic of Germany.
SO JOURNAL OF NEURAL TRANSMISSION, (2002 Jul) 109 (7-8) 1081-7.
Journal code: 9702341. ISSN: 0300-9564.
CY Austria
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20020712
Last Updated on STN: 20020712
AB SUMMARY: Studies in transgenic mouse models of Alzheimer's disease suggested the development of a vaccine that would induce the production of **antibodies** against **amyloid-beta** (Abeta) peptide, which in turn would stimulate microglia to phagocytose and remove senile plaques. However, some patients in the human **clinical trials** developed symptoms of brain inflammation, demonstrated by lymphocyte infiltration and elevated protein levels. These parameters are indicative of a breakdown of the blood-brain-barrier and entry of T-cells into the brain. Abeta-specific activated T-helper cells have the potential to amplify the existing pro-inflammatory conditions that are present in the brains of Alzheimer's disease patients. Cytotoxic T-cells might even attack the **amyloid** precursor protein which is present on the surface of many cells, including neurons. Before undertaking further vaccination trials there is a need to re-assess the risks associated with Abeta vaccination and with the therapeutic containment of a neuroinflammatory response. These risks may not be justified in the light of recent studies which have shown the efficacy of conventional, low-risk treatments in slowing the progress of AD.

enablement humans.

L12 ANSWER 1 OF 1 MEDLINE
AN 2001419655 MEDLINE
DN 21352991 PubMed ID: 11438712
TI **Peripheral** anti-A beta **antibody alters** **CNS** and **plasma** A beta clearance and decreases brain A beta burden in a mouse model of Alzheimer's disease.
AU DeMattos R B; Bales K R; Cummins D J; Dodart J C; Paul S M; Holtzman D M
CS The Center for the Study of Nervous System Injury, Washington University School of Medicine, 660 South Euclid Avenue, Box 8111, St. Louis, MO 63110, USA.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2001 Jul 17) 98 (15) 8850-5.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010903
Last Updated on STN: 20020420
Entered Medline: 20010830
AB Active immunization with the amyloid beta (A beta) peptide has been shown to decrease brain A beta deposition in transgenic mouse models of Alzheimer's disease and certain peripherally administered anti-A beta **antibodies** were shown to mimic this effect. In exploring factors that alter A beta metabolism and clearance, we found that a monoclonal **antibody** (m266) directed against the central domain of A beta was able to bind and completely sequester **plasma** A beta. **Peripheral** administration of m266 to PDAPP transgenic mice, in which A beta is generated specifically within the central nervous system (**CNS**), results in a rapid 1,000-fold increase in **plasma** A beta, due, in part, to a change in A beta equilibrium between the **CNS** and **plasma**. Although **peripheral** administration of m266 to PDAPP mice markedly reduces A beta deposition, m266 did not bind to A beta deposits in the brain. Thus, m266 appears to reduce brain A beta burden by altering **CNS** and **plasma** A beta clearance.

L3 ANSWER 1 OF 8 MEDLINE
AN 2002088343 MEDLINE
DN 21591165 PubMed ID: 11816797
TI Potential treatment opportunities for Alzheimer's disease through inhibition of secretases and Abeta immunization.
AU Schenk D; Games D; Seubert P
CS Elan Pharmaceuticals, San Francisco, CA 94080, USA..
dale.schenk@elancorp.com
SO JOURNAL OF MOLECULAR NEUROSCIENCE, (2001 Oct) 17 (2) 259-67. Ref: 63
Journal code: 9002991. ISSN: 0895-8696.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200205
ED Entered STN: 20020131
Last Updated on STN: 20020508
Entered Medline: 20020507
AB Research over the past ten years on Alzheimer's disease has pursued many opportunities. Notable amongst the various approaches are efforts related to the "amyloid hypothesis." This hypothesis posits that the **beta amyloid** peptide causes the extensive neuropathology and clinical decline associated with the disease. Extensive research in this area has shown that the **beta amyloid** peptide is produced by proteases termed "secretases" and it has been shown that blockade of secretase functions reduce the amount of **beta amyloid** peptide produced. An additional approach to reduce **beta amyloid**, through an increase in clearance mechanisms, is to immunize with the peptide itself and induce an antibody response. The specifically elicited antibodies then bind to and stimulate clearance of the peptide from the brain. These findings have stimulated several approaches to develop novel therapeutic strategies to treat Alzheimer's disease that either are about or have entered the clinic.